Sleep Medicine Reviews 18 (2014) 261–271

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

A review of the effects of pregabalin on sleep disturbance across multiple clinical conditions

Thomas Roth [a,*], Lesley M. Arnold [b,1], Diego Garcia-Borreguero [c,2], Malca Resnick [d,3], Andrew G. Clair [d,4]

[a] Division of Sleep Medicine and Research Center, Henry Ford Health System, 2799 West Grand Boulevard, Detroit, MI 48202, USA
[b] Women's Health Research Program, University of Cincinnati, 260 Stetson Street, Suite 3200, Cincinnati, OH 45219, USA
[c] Sleep Research Institute, Alberto Alcocer 19, 28036 Madrid, Spain
[d] Pfizer Inc., 235 East 42nd Street, New York, NY 10017, USA

ARTICLE INFO

Article history:
Received 20 February 2013
Received in revised form
12 July 2013
Accepted 30 July 2013
Available online 9 October 2013

Keywords:
Pregabalin
Sleep disturbance
Polysomnography
Patient-report

SUMMARY

Pregabalin is approved for the treatment of a variety of clinical conditions and its analgesic, anxiolytic and anticonvulsant properties are well documented. Pregabalin's effects on sleep, however, are less well known. This review summarizes the published data on the effects of pregabalin on sleep disturbance associated with neuropathic pain, fibromyalgia, restless legs syndrome, partial onset seizures and general anxiety disorder. The data demonstrate that pregabalin has a positive benefit on sleep disturbance associated with several different clinical conditions. Polysomnographic data reveal that pregabalin primarily affects sleep maintenance. The evidence indicates that pregabalin has a direct effect on sleep that is distinct from its analgesic, anxiolytic and anticonvulsant effects.

Introduction

Pregabalin (Lyrica) is an $\alpha_2\delta$ ligand approved for the treatment of a variety of clinical conditions. It is approved for certain types of neuropathic pain in the United States (US) and European Union (EU), fibromyalgia (FM) in the US, generalized anxiety disorder (GAD) in the EU, and partial onset seizures in the US and EU. Consequently, there are clinical trial data for pregabalin across several clinical conditions. While the pain- and anxiety-reducing effects of pregabalin are widely documented, its effects on sleep are less well known. The purpose of this review is to summarize all the published data on the effects of pregabalin on sleep in several different clinical conditions associated with sleep disturbance. Pubmed and Pfizer databases were used to identify published papers that reported on the effects of pregabalin treatment on any outcome measure (primary or secondary) related to the assessment of sleep in healthy volunteers or in patients with neuropathic pain, FM, restless legs syndrome (RLS), partial onset seizures or GAD.

In addition to polysomnography (PSG) and actigraphy, the studies in this review include a variety of patient-reported measures that examined the effects of pregabalin on sleep. These include the daily sleep interference scale (DSIS), the daily sleep quality diary (DSQD), the medical outcomes study-sleep scale (MOS-SS) and the Hamilton anxiety (HAM-A) or depression (HAM-D) instruments. The DSIS rates sleep during the previous 24 h on an 11-point numeric rating scale ranging from 0 = "pain did not interfere with sleep" to 10 = "pain completely interfered with sleep", while the DSQD rates sleep on a scale from 0 = "best possible sleep" to 10 = "worst possible sleep". The MOS-SS questionnaire rates specific aspects of sleep and provides an overall sleep problems index [1]. Greater impairment is indicated by higher (sleep disturbance, snoring, awaken short of breath and somnolence) or lower (sleep adequacy and quantity of sleep) subscale scores. These scores range from 0 to 100, with the exception of sleep quantity, which is measured in hours. The HAM-A insomnia factor is characterized by difficulty in falling or staying asleep and the presence of nightmares. The severity of these symptoms is indicated by an insomnia factor score from 0 = "none" to 4 = "very

* Corresponding author. Tel.: +1 313 916 5171; fax: +1 313 916 5167.
E-mail addresses: troth1@hfhs.org, troth1@smtpgw.is.hfh.edu (T. Roth), Lesley.Arnold@uc.edu (L.M. Arnold), dgb@iis.es (D. Garcia-Borreguero), malca.resnick@pfizer.com (M. Resnick), andrew.clair@pfizer.com (A.G. Clair).
[1] Tel.: +1 513 558 4622; fax: +1 558 4280.
[2] Tel.: +34 913 454 129; fax: +34 913 459 095.
[3] Tel.: +1 212 733 1802; fax: +1 646 441 4326.
[4] Tel.: +1 212 733 5991; fax: +1 646 441 5715.

1087-0792/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.smrv.2013.07.005

Glossary of terms

DPN	diabetic peripheral neuropathy
DSIS	daily sleep interference scale
DSQD	daily sleep quality diary
EU	European Union
FM	fibromyalgia
GAD	generalized anxiety disorder
HAM-A	Hamilton anxiety instrument
HAM-D	Hamilton depression instrument
MOS-SS	medical outcomes study-sleep scale
PHN	post-herpetic neuralgia
PSG	polysomnography
REM	rapid eye movement
RLS	restless legs syndrome
SCI	spinal cord injury
US	United States

severe" [2]. The HAM-D insomnia factor is the sum of three scores related to difficulty falling asleep (early insomnia), difficulty staying asleep (middle insomnia) and frequent early morning awakenings (late insomnia). The total sum of these three items ranges from 0 to 6, with higher scores indicating greater sleep disturbance [3].

For the purposes of this review, pregabalin was considered as having an effect on a specific sleep measure (i.e., "improved", "increased" or "decreased") only if that effect was statistically significantly different ($p < 0.05$) from placebo (for placebo-controlled trials) or baseline (for observational studies). For changes that were not statistically significantly different from placebo or baseline, pregabalin was considered as having no effect.

Neuropathic pain

Neuropathic pain results from a primary lesion or dysfunction in the nervous system itself [4] and is often accompanied by sleep disturbance. Patients commonly report difficulties both in initiating and maintaining sleep that adversely affect function and quality of life [5–7].

Diabetic peripheral neuropathy and post-herpetic neuralgia

Pain-related sleep interference is reported in approximately 57% and 40% of diabetic peripheral neuropathy (DPN) [5] and post-herpetic neuralgia (PHN) [7] patients, respectively. PSG has revealed decreased sleep efficiency, fragmented sleep and less slow-wave sleep compared with healthy controls in the literature [8].

One DPN study used PSG to examine pregabalin's effects on sleep [9]. Patients received placebo (8 d), followed by 300 mg/d pregabalin (14 d) and 600 mg/d pregabalin (14 d). PSG was performed following each treatment period. Patients had more non-rapid eye movement (non-REM) sleep (+27.5 min) and less rapid eye movement (REM) sleep (−18.5 min) following treatment with 300 mg/d pregabalin compared with placebo. This was also evident following treatment with 600 mg/d pregabalin, where non-REM sleep was increased (+56.8 min) and REM sleep was decreased (−18.1 min) compared with placebo. Additionally, improvements in total sleep time (+38.7 min), sleep efficiency (+8.1%) and wake time after sleep onset (−33.7 min) were observed following 600 mg/d pregabalin treatment, but not after treatment with 300 mg/d pregabalin. It should be noted that the effects of pregabalin on individual sleep stages were not reported in this DPN study.

Other placebo-controlled studies of DPN and PHN used patient-reported assessments of sleep (see Table 1). In DPN studies, 300 and 600 mg/d pregabalin improved DSIS scores, and improvements were evident at the first point of evaluation (after one week of treatment) [10–15]. Lower doses (75 and 150 mg/d) did not differ from placebo. One study included the MOS-SS to assess whether sleep and higher doses of pregabalin (300 or 600 mg/d) improved sleep disturbance, quantity of sleep, sleep adequacy and the overall sleep problems index [15]. Other MOS-SS subscales were not improved. In PHN studies, all doses of pregabalin (150, 300 and 600 mg/d and flexible 150–600 mg/d) improved DSIS score, and improvements were evident after one week of treatment [16–20]. One study included the MOS-SS to assess sleep and found that pregabalin treatment (300 and 600 mg/d) improved the overall sleep problems index [17]. Other MOS-SS subscales were not analyzed. In three studies enrolling both DPN and PHN patients, all doses of pregabalin (600 mg/d and flexible 150–600 mg/d) improved DSIS score and, in most instances, improvements were evident by week one [21–23]. One study included the MOS-SS to assess sleep and found that both pregabalin treatment arms (600 mg/d and flexible 150–600 mg/d) improved the sleep disturbance subscale and overall sleep problems index [21]. Other MOS-SS subscales were not improved.

Neuropathic pain due to spinal cord injury

Nearly 40% of spinal cord injury (SCI) patients report frequent difficulties in both falling and staying asleep [6]. Two placebo-controlled trials of pregabalin in SCI patients included measures of pain-related sleep interference [24,25] (see Table 1). In both trials, pregabalin improved DSIS scores after one week of treatment. Pregabalin also improved MOS-SS sleep disturbance, sleep quantity and overall sleep problems index scores in both trials. In one trial, pregabalin-treated patients were more likely (odds ratio = 2.81) to report having "optimal sleep" compared with placebo [25]. Remaining MOS-SS subscales were not improved in either trial. Both trials employed flexible-dose pregabalin (150–600 mg/d) for 12–16 wk. There were no PSG studies in this patient population.

Neuropathic pain of other etiologies

Pregabalin's effects on pain-related sleep interference have also been examined in studies of neuropathic pain due to cervical or lumbar radiculopathy [26,27], stroke [28], trauma [29], cancer [30], trigeminal neuralgia [31] and human immunodeficiency virus (HIV) infection [32] (see Table 1). Pregabalin improved the DSIS score in placebo-controlled trials of post-traumatic peripheral neuropathic pain [29], but not in trials of lumbar radiculopathy [27], post-stroke pain [28] or HIV infection [32]. DSIS score was not assessed in observational studies of cervical/lumbar radiculopathy [26], trigeminal neuralgia [31] or neuropathic cancer pain [30]. Pregabalin treatment also resulted in improvements over placebo or baseline (observational studies) on MOS-SS sleep disturbance [26,27,29–31], sleep quantity [26–28,30,31], somnolence [31], snoring [28], shortness of breath [31], sleep adequacy [28–31] and overall sleep problems index [28–31].

In trials of neuropathic pain of different/mixed etiologies, pregabalin improved DSIS score in trials of DPN, PHN and chemotherapy-induced neuropathic pain [33]; DPN, PHN and post-traumatic peripheral pain [34]; DPN, PHN and neuropathic pain due to "ill-defined disorder" [35]; DPN, PHN, radiculopathy and trigeminal neuralgia [36]; and peripheral neuropathic pain due to a broad range of etiologies [37] (see Table 1). One study included the MOS-SS to assess sleep and showed that pregabalin improved both the sleep disturbance and quantity of sleep subscales [34]. Other MOS-SS subscales were not improved. Overall, it is unknown whether pregabalin improved sleep disturbance in specific patient populations because these studies were not powered for individual

Table 1
DSIS scores at study endpoint in trials of pregabalin for neuropathic pain.[a]

Study	Duration	Pregabalin treatment arms	Versus placebo		
			Treatment difference	95% CI	*p*-Value
DPN					
Lesser et al. (2004) [11]	6 wk	150 mg/d	−0.43	(−1.04, 0.18)	NS
		600 mg/d	−1.15	(−1.75, −0.55)	<0.001
Rosenstock et al. (2004) [12]	5 wk	75 mg/d	−0.42	(−1.02, 0.17)	NS
		300 mg/d	−1.30	(−1.89, −0.71)	<0.001
		600 mg/d	−1.55	(−2.14, −0.96)	<0.001
Richter et al. (2005) [10]	8 wk	300 mg/d	−1.54	(−2.28, −0.80)	<0.001
Arezzo et al. (2008) [14]	12 wk	150 mg/d	−0.45	(−1.05, 0.15)	NS
		300 mg/d	−0.62	(−1.22, −0.02)	NS
		600 mg/d	−1.01	(−1.60, −0.41)	0.003
Tolle et al. (2008) [13]	13 wk	600 mg/d	−1.08	(−1.75, −0.41)	0.002
Satoh et al. (2011) [15]	13 wk	300 mg/d	−0.85	(−1.25, −0.46)	<0.001
		600 mg/d	−0.63	(−1.19, −0.07)	0.027
PHN					
Dworkin et al. (2003) [17]	8 wk	150 mg/d	−1.11	(−1.71, −0.51)	<0.001
		300 mg/d	−1.43	(−2.04, −0.82)	<0.001
Sabatowski et al. (2004) [16]	8 wk	300/600 mg/d[b]	−1.58	(−2.19, −0.97)	<0.001
van Seventer et al. (2006) [18]	13 wk	150 mg/d	−1.03	(−1.62, −0.44)	<0.001
		300 mg/d	−1.26	(−1.84, −0.68)	<0.001
		600 mg/d	−1.93	(−2.52, −1.34)	<0.001
Stacey et al. (2008) [19]	4 wk	300 mg/d	−0.75	(−1.23, −0.27)	0.002
		150–600 mg/d[c]	−0.93	(−1.40, −0.47)	<0.001
Ogawa et al. (2010) [20]	13 wk	150 mg/d	−0.76	(−1.23, −0.30)	0.001
		300 mg/d	−0.81	(−1.27, −0.34)	0.001
		600 mg/d	−0.94	(−1.40, −0.49)	<0.001
DPN/PHN					
Freynhagen et al. (2005) [21]	12 wk	600 mg/d	−1.48	(−2.17, −0.79)	<0.001
		150–600 mg/d[c]	−1.36	(−2.04, −0.68)	<0.001
Baron et al. (2008) [22]	8 wk	150–600 mg/d[c]	−0.50	(−0.93, −0.07)	0.023
Guan et al. (2011) [23]	4 wk	150–600 mg/d[c]	−2.2[d]	(−2.50, −1.80)	<0.001
Spinal cord injury					
Siddall et al. (2006) [24]	12 wk	150–600 mg/d[c]	−1.37	(−1.97, −0.77)	<0.001
Cardenas et al. (2013) [25]	16 wk	150–600 mg/d[c]	−1.08	(−1.60, −0.56)	<0.001
Lumbar radiculopathy					
Baron et al. (2010) [27]	9 wk	150–600 mg/d[c]	−0.19	(−0.56, 0.19)	NS
HIV					
Simpson et al. (2010) [32]	14 wk	150–600 mg/d[c]	−0.19	(−0.73, 0.34)	NS
Stroke					
Kim et al. (2011) [28]	12 wk	150–600 mg/d[c]	−0.10	(−0.60, 0.40)	NS
Trauma (peripheral)					
Van Seventer et al. (2010) [29]	8 wk	150–600 mg/d[c]	−0.79	(−1.25, −0.34)	0.001
Multiple etiologies					
Lyrica Study Group (2006) [36]	12 wk	150–600 mg/d[c]	−3.1[d]	(−3.60, −2.60)	<0.001
Moon et al. (2010) [34]	8 wk	150–600 mg/d[c]	−0.51	(−0.96, −0.07)	0.024
Xochilcal-Morales et al. (2010) [33]	8 wk	150–600 mg/d[c]	−4.02[d]	(−4.24, −3.80)	<0.001
Anastassiou et al. (2011) [35]	9 wk	150–600 mg/d[c]	−0.71	(−1.18, −0.24)	0.003
Gilron et al. (2011) [37]	3 wk	150–600 mg/d[c]	−1.62[d]	N/A	<0.001
Toelle et al. (2012)[e] [38]	6 wk	150–600 mg/d[c]			
DPN			−3.9[d]	N/A	<0.05
Cancer pain			−3.8[d]	N/A	<0.05
Back pain			−4.0[d]	N/A	<0.05

CI: confidence interval; DPN: diabetic peripheral neuropathy; DSIS: daily sleep interference scale; NS: not significant; PHN: post-herpetic neuralgia.
[a] DSIS scores rates range from 0 = "pain did not interfere with sleep" to 10 = "pain completely interfered with sleep". Negative values indicate improvement.
[b] Pregabalin dosage was 600 mg/d for patients with creatinine clearance >60 mL/min and 300 mg/d for patients with >30 mL/min but ≤60 mL/min.
[c] Indicates flexible dosing.
[d] Value is change from baseline, not difference from placebo, since data are from an open-label or non-interventional study lacking a placebo control label or non-interventional study lacking a placebo control.
[e] Toelle et al. broke down the patients based on the cause of neuropathic pain (i.e., DPN, cancer, or back pain) and analyzed them as separate groups.

disorders. The percentage of patients with PHN or DPN in each study was: 96% [33], 75% [36], 68% [34], 60% [37] and 24% [35], respectively. In one six-week observational trial in patients with DPN, neuropathic cancer pain or neuropathic back pain, however, pregabalin (150–600 mg/d) improved DSIS scores in each specific patient population [38].

Direct effects of pregabalin on sleep in neuropathic pain

In an eight-week open-label trial of pregabalin in patients with neuropathic pain of any origin, improvements in patient-reported sleep quality were marginally ($r = 0.36$) related to pain relief [39]. In the aforementioned eight-week placebo-controlled trial of pregabalin for post-traumatic neuropathic pain, however, a clear relationship between pain relief and improvements in sleep was observed [40]. Specifically, pain relief was positively associated with improvements in DSIS score, MOS-SS sleep disturbance score and the MOS-SS overall sleep problems index. Improvements in MOS-SS sleep disturbance score were present even in patients who did not experience pain relief, suggesting that pregabalin has, at least in part, a direct effect on sleep itself.

Practice points

In trials of neuropathic pain:

1) neuropathic pain was frequently associated with disturbed sleep and decreased slow-wave sleep;
2. polysomnography demonstrated that pregabalin (600 mg/d) improved total sleep time, sleep efficiency and wake time after sleep onset (diabetic peripheral neuropathy patients);
3. pregabalin consistently improved patient-reported assessments of sleep quality that, generally, were evident after one week and were sustained throughout the treatment period;
4. correlation analyses suggest that pregabalin has, at least in part, a direct effect on sleep itself.

FM

FM is characterized by widespread pain and tenderness, and is associated with sleep disturbance, fatigue, anxiety, depression and memory/cognitive problems [41]. In recognition of the prevalence and impact of sleep disturbance, the 2010 clinical diagnostic criteria for FM includes sleep problems as a key component [41]. Though the specific sleep abnormality associated with FM has not been fully elucidated, patients often report difficulty falling asleep, frequent awakenings and unrefreshing sleep [42]. PSG confirms delayed sleep onset, more frequent arousals and decreased sleep efficiency compared with healthy controls. PSG also reveals an alpha delta sleep pattern during non-REM sleep in many cases [43,44].

In a placebo-controlled, crossover PSG study in FM patients, pregabalin treatment (150–450 mg/d for 29 d) improved wake time after sleep onset, total sleep time, latency to persistent sleep, sleep efficiency, the number of awakenings after sleep onset and the amount of slow-wave sleep relative to placebo [45]. Patient reports paralleled PSG data, with improvements in wake time after sleep onset, latency to sleep onset, total sleep time and sleep quality.

Other placebo-controlled trials of pregabalin for the treatment of FM [46–49] (see Table 2) used patient-reported measures of sleep. A meta-analysis of these trials showed that pregabalin (8–14 wk) improved DSQD scores at doses of 300, 450 and 600 mg/d [50]. Improvement was evident after one week and, generally, was sustained throughout the treatment period. The meta-analysis also demonstrated that all doses of pregabalin improved MOS-SS sleep disturbance, awakening short of breath or with headache, quantity of sleep and sleep adequacy subscales, as well as the overall sleep problems index. In contrast, snoring and somnolence subscales were significantly worse. In the two 13–14-wk trials, pregabalin (450 and 600 mg/d) was associated with clinically important improvements in DSQD and MOS-SS sleep disturbance scores [47,48,51].

Direct effects of pregabalin on sleep in FM

A high correlation ($r \geq 0.65$) between pain relief and improvement in sleep quality was demonstrated for all doses of pregabalin in the two 13–14-wk FM trials [47,48,51]. All doses also exhibited moderate ($r = 0.30–0.51$) correlations between pain relief and changes in both the MOS-SS sleep disturbance subscale and the overall sleep problems index. Likewise, analysis of all four trials demonstrated a significant treatment by sleep interaction, with greater pain relief at endpoint associated with more severe baseline sleep disturbance scores [52]. In these trials, moderate and

Table 2
Effects of pregabalin on disturbed sleep in patients with FM.

Study	Duration	Pregabalin treatment arms	Statistically significant improvements (versus placebo)
Crofford et al. (2005) [46]	8 wk	150 mg/d	**DSQD**[a]**:** no improvement; **MOS-SS**[b]**:** improved sleep problems index
		300 mg/d	**DSQD:** decreased by −0.6; **MOS-SS:** improved sleep problems index
		450 mg/d	**DSQD:** decreased by −1.3; **MOS-SS:** improved sleep problems index
Mease et al. (2008) [47]	13 wk	300 mg/d	**DSQD:** decreased by −0.9; **MOS-SS:** improved sleep problems index, decreased sleep disturbance, increased quantity of sleep, increased sleep adequacy
		450 mg/d	**DSQD:** decreased by−1.0; **MOS-SS:** improved sleep problems index, decreased sleep disturbance, decreased abrupt awakening, increased quantity of sleep, increased sleep adequacy
		600 mg/d	**DSQD:** decreased by −1.2; **MOS-SS:** improved sleep problems index, decreased sleep disturbance, decreased abrupt awakening, increased quantity of sleep
Arnold et al. (2008) [48]	14 wk	300 mg/d	**DSQD:** decreased by −0.7; **MOS-SS**[a]**:** improved sleep problems index
		450 mg/d	**DSQD:** decreased by −1.1; **MOS-SS:** improved sleep problems index
		600 mg/d	**DSQD:** decreased by −1.4; **MOS-SS:** improved sleep problems index
Pauer et al. (2011) [49]	14 wk	300 mg/d	**DSQD:** decreased by −0.5; **MOS-SS**[c]**:** decreased sleep disturbance
		450 mg/d	**DSQD:** decreased by −0.8; **MOS-SS:** decreased sleep disturbance
		600 mg/d	**DSQD:** decreased by −1.0; **MOS-SS:** decreased sleep disturbance
Roth et al. (2012) [45]	8 wk[d]	300–450 mg/d[e]	**PSG:** decreased WASO (−19 min), increased total sleep time (+25 min), decreased latency to persistent sleep (−7 min), increased sleep efficiency (+5%), reduced the NAASO (−2), increased the amount of slow-wave sleep (+2%); **sleep quality**[f]: improved (+0.9); **SSQ:** decreased WASO (−10 min), decreased latency to sleep onset (−6 min), increased total sleep time (>25 min)

DSQD: daily sleep quality diary; FM: fibromyalgia; MOS-SS: medical outcomes study-sleep scale; NAASO: number of awakenings after sleep onset; PSG: polysomnography; SSQ: subjective sleep questionnaire; WASO: wake time after sleep onset.

[a] DSQD scores range from 0 = "best possible sleep" to 10 = "worst possible sleep".

[b] The only MOS-SS item that was evaluated was the overall sleep problems index.

[c] The only MOS-SS item that was evaluated was the sleep disturbance subscale.

[d] Crossover design where patients received either placebo or pregabalin for four weeks, followed by a two-week washout period, followed by an additional four-week period where patients received either placebo or pregabalin.

[e] Indicates flexible dosing.

[f] Scores range from 0 = "worst sleep" to 10 = "best sleep".

substantial levels of pain relief at endpoint (≥30% and ≥50% decreases in baseline pain score, respectively) resulted in attainment of MOS-SS sleep disturbance and overall sleep problems index scores comparable with the general population [53]. Additionally, severity of daily pain was modestly negatively correlated with total sleep time ($\rho = -0.236$), and modestly positively correlated with latency to persistent sleep ($\rho = 0.249$) and total wake time ($\rho = 0.270$) in the PSG study. [45]

Mediation analysis of the two 13–14-wk trials estimated that a substantial percentage (42–60%) of the improvement in patient-reported sleep quality was due to a direct effect of pregabalin treatment on sleep itself, with the remainder indirectly due to improvements in pain [47,48,51]. Likewise, it was estimated that 66–80% of the improvement in MOS-SS sleep disturbance score was a direct effect of pregabalin treatment.

Practice points

In trials of fibromyalgia:

1) polysomnography demonstrates that pregabalin (150–450 mg/d) improved wake time after sleep onset, total sleep time, latency to persistent sleep, sleep efficiency, the number of awakenings after sleep onset and increased the amount of slow-wave sleep;
2) pregabalin (300–600 mg/d) consistently improved patient-reported assessments of sleep quality that, generally, were evident after one week and were sustained throughout the treatment period;
3) mediation analyses suggest that pregabalin has, at least in part, a direct effect on sleep itself.

RLS/Willis-Ekbom disease

RLS is a neurological disorder characterized by the urge to move the legs and is usually accompanied by discomfort typically while at rest, occurring mostly in the evening and relieved by movement [54]. Sleep disturbance is a hallmark of RLS that impacts patient quality of life. Patients often report problems with sleep onset (69%) and frequent awakenings (60%) [55]. PSG demonstrates poor sleep efficiency and substantial wake time after sleep onset [56,57].

In one RLS trial, pregabalin (150–600 mg/d; flexible) increased PSG-assessed slow-wave sleep and non-REM sleep compared with placebo [58]. Pregabalin also decreased both stage 1 sleep and wake time after sleep onset [58]. There was no effect of pregabalin on total sleep time, sleep efficiency, sleep latency or REM sleep. Though not evident in the PSG trial, actigraphy revealed that higher doses of pregabalin (300–450 mg/d) increased total sleep time and sleep efficiency compared with placebo [59]. These effects, however, were not seen at doses of 50–150 mg/d. It is not clear what accounts for the discrepancy between the PSG and the actigraphy data.

Pregabalin improved various MOS-SS subscales in both RLS trials [58,59] (see Table 3). In addition, improvements in sleep were reported via a patient-reported sleep questionnaire [59]. However, patient-reported improvements in sleep disturbance did not exhibit a dose–response relationship.

In both studies pregabalin significantly improved symptoms of RLS as assessed by the International restless legs scale total score. Pregabalin has also been shown to decrease the occurrence of period limb movements, as assessed by the periodic limb movement index, in RLS patients [58]. Alleviation of motor dysfunction is thought to result in improved sleep in RLS patients, though the degree to which alleviation of motor dysfunction affects sleep is still a matter of debate. Indeed, dopaminergic agents generally normalize periodic limb movements in RLS patients without improving sleep parameters. This suggests that pregabalin causes a direct improvement in sleep itself in RLS patients, apart from its effects on motor dysfunction.

Practice points

In trials of RLS:

1) polysomnography demonstrated that pregabalin (150–450 mg/d) decreased stage 1 sleep and wake time after sleep onset, while increasing the amount of slow-wave sleep;
2) pregabalin (300–450 mg/d) increased actigraphy-based total sleep time and sleep efficiency;
3) improvements in patient-reported assessments of sleep were inconsistent;
4) pregabalin significantly improved International restless legs scale and periodic limb movement index scores.

Table 3
Effects of pregabalin on disturbed sleep in patients with RLS.

Study	Duration	Pregabalin treatment arms	Statistically significant improvements (versus placebo)
Allen et al. (2004) [59]	6 wk	50 mg/d	**MOS-SS:** increased sleep adequacy; **SSQ:** increased hours of sleep, decreased WASO, increased quality of sleep; **actigraphy:** no improvements
		100 mg/d	No improvements
		150 mg/d	**MOS-SS:** improved sleep problems index, increased sleep quantity; **SSQ:** increased hours of sleep, increased quality of sleep; **actigraphy:** increased total sleep time (+70 min)
		300 mg/d	**MOS-SS and SSQ:** no improvements; **actigraphy:** increased total sleep time (+66 min), increased sleep efficiency (+7%)
		450 mg/d	**MOS-SS:** improved sleep problems index, decreased sleep disturbance; **SSQ:** decreased sleep latency, increased hours of sleep, increased quality of sleep; **actigraphy:** increased total sleep time (+59 min), increased sleep efficiency (+7%)
Garcia-Borreguero et al. (2010) [58]	12 wk	150–450 mg/d[a]	**MOS-SS:** decreased sleep disturbance, increased sleep adequacy, increased sleep quantity; **PSG:** decreased WASO (−46 min), decreased stage 1 sleep (−4%), increased stage 2 sleep (+4%), increased stage 3 sleep (+6%), increased stage 4 sleep (+16 min), increased amount of slow-wave sleep (+40 min), increased non-REM sleep (+51 min)

MOS-SS: medical outcomes study-sleep scale; PSG: polysomnography; RLS: restless legs syndrome; SSQ: subjective sleep questionnaire; WASO: wake time after sleep onset.
[a] Indicates flexible dosing.

Table 4
Effects of pregabalin on disturbed sleep in patients with partial onset seizures.

Study	Duration	Pregabalin treatment arms	Statistically significant improvements
deHass et al. (2007) [65]	4 wk	300 mg/d	**MOS-SS:** decreased sleep disturbance, increased quantity of sleep; **PSG:** decreased NAASO (−3.9)[a]
Romigi et al. (2009) [64]	12 wk	150–375 mg/d[b]	**PSG:** increased REM sleep (+6%), decreased stage N2 sleep (−6.5%)[c]
Lee et al. (2009) [67]	12 wk	150–600 mg/d[b]	**DSIS[d]:** improved by −0.45[a]
Ryvlin et al. (2010) [71]	21 wk	150–600 mg/d[b]	No improvements on any MOS-SS subscale
Sancho et al. (2010) [69]	6 mo	150–600 mg/d[b]	**MOS-SS:** improved all subscales except abrupt awakening[c]
Rivera-Castano et al. (2012) [68]	21 wk	150–600 mg/d[b]	**MOS-SS:** decreased sleep disturbance, increased quantity of sleep[c]
Tsounis et al. (2011) [70]	12 wk	150–600 mg/d[b]	No improvements on any MOS-SS subscale
Bazil et al. (2012) [66]	2 wk	300 mg/d	**PSG:** increased slow-wave sleep (+6%), decreased stage N1 sleep (−4%)[a]

DSIS: daily sleep interference scale; MOS-SS: medical outcomes study-sleep scale; NAASO: number of awakenings after sleep onset; PSG: polysomnography; REM: rapid eye movement.
[a] Compared with placebo.
[b] Indicates flexible dosing.
[c] Compared with baseline, since data are from an observational/open-label study lacking a placebo control.
[d] DSIS scores range from 0 = "pain did not interfere with sleep" to 10 = "pain completely interfered with sleep". Negative values indicate improvement.

Partial epilepsy

Sleep disturbance occurs more frequently among epilepsy patients compared with age- and gender-matched controls, and the presence of sleep disturbance is associated with poorer quality of life than the presence of partial epilepsy alone [60]. PSG reveals sleep fragmentation, with an increased number of awakenings/arousals and an overall decrease in sleep efficiency [61,62]. Such sleep disturbance may be related to mood disturbances, nocturnal seizures or even, in some cases, treatment with anti-epileptic drugs themselves [63].

Most studies of pregabalin in patients with partial onset seizures (see Table 4) were open-label and used only patient-reported measures of sleep. Three small trials, however, used PSG to assess sleep. In a three-month open-label PSG trial, pregabalin treatment (150–375 mg/d) increased REM sleep and decreased stage N2 sleep compared with baseline. [64] No significant correlation was found between increased REM sleep and seizure reduction, suggesting that improvements in sleep were not due to pregabalin's anticonvulsant activity. No improvements were observed for other PSG items including total sleep time, sleep efficiency, sleep latency, wake time after sleep onset and the amount of slow-wave sleep. In another four-week trial of 300 mg/d pregabalin, the only PSG item that improved versus placebo was the number of awakenings [65]. PSG assessment in this trial; however, was limited by substantial placebo effects. The final trial was a double-blind, placebo-controlled crossover study in patients with partial seizures who also met criteria for a clinical diagnosis of insomnia [66]. In this study, two-week treatment with 300 mg/d pregabalin increased the percentage of slow-wave sleep and decreased stage 1 sleep compared with placebo. There were no effects on REM sleep, stage 2 sleep, sleep latency or sleep efficiency.

One double-blind, placebo-controlled study used the DSIS and modest improvements were reported following 12-wk of treatment with pregabalin (flexible 150–600 mg/d) [67]. Open-label studies assessed sleep using the MOS-SS, though findings were inconsistent. In one 21-wk trial, patients receiving pregabalin (flexible 150–600 mg/d) exhibited modest improvements only on the MOS-SS sleep disturbance and quantity of sleep subscales [68]. In a six-month observational study, pregabalin improved all MOS-SS subscales, except abrupt awakening, at months three and six [69]. In contrast, no improvements on any MOS-SS subscale were reported in 12-wk [70] and 21-wk [71] trials of pregabalin (flexible 150–600 mg/d). In the latter study, however, baseline MOS-SS scores were similar to the general population and not indicative of disturbed sleep.

Practice points

In trials of partial epilepsy:

1) the effects of pregabalin are inconsistent across trials, with polysomnography reports of increased rapid eye movement sleep and reports of increased slow-wave sleep in conjunction with decreased stage 1 sleep. In terms of overall sleep induction and maintenance parameters, there are no consistent effects found with either polysomnography or patient reports.

Generalized anxiety disorder

Sleep disturbance is a diagnostic criterion for GAD, with insomnia present in 50% of patients [72]. The onset of sleep disturbance is often concurrent with, or occurs after, the onset of GAD [73]. PSG reveals increased sleep latency, reduced total sleep time and sleep efficiency, and a low percentage of slow-wave sleep. [74,75]

Several studies have evaluated the efficacy of pregabalin in patients with GAD [76–83]. In an eight-week study using the MOS-SS, pregabalin treatment (flexible 300–600 mg/d) improved the sleep disturbance subscale and overall sleep problems index compared with placebo [76]. Remaining MOS-SS subscales were not improved. Most studies; however, used the insomnia factor of the HAM-A or HAM-D instruments to assess sleep disturbance in the GAD population (see Table 5).

Pooled analysis of seven GAD trials showed that pregabalin improved HAM-A insomnia factor at all doses examined. Change at endpoint was −1.1 (150 mg/d), −1.3 (300–450 mg/d) and −1.3 (600 mg/d) compared with −0.8 for placebo [84]. In a separate analysis of these same trials, higher doses of pregabalin (300–600 mg/d) improved HAM-D insomnia factor in patients with high levels of insomnia (HAM-D insomnia score >3) at baseline [85]. All doses of pregabalin resulted in modest improvements in patients with low baseline insomnia levels as well. Pregabalin treatment also resulted in a greater percentage of patients achieving remission from insomnia (HAM-D insomnia score <2) compared with placebo (pregabalin 600 mg/d = 43.3%; pregabalin 300–450 mg/d = 34.6%; placebo = 29.4%). Pregabalin's effect on anxiety in these patients was unrelated to baseline insomnia severity.

Table 5
HAM-A and HAM-D insomnia scores in trials of pregabalin for GAD.

Study	Duration	Pregabalin treatment arms	Versus placebo		
			Treatment difference	95% CI	*p*-Value
Feltner et al. (2003) [77]	4 wk	150 mg/d			
		HAM-A[a]	−0.35	(−0.66, −0.03)	0.030
		HAM-D[b]	−0.53	(−1.04, −0.01)	0.046
		600 mg/d			
		HAM-A	−0.49	(−0.81, −0.18)	0.002
		HAM-D	−0.83	(−1.35, −0.31)	0.002
Pande et al. (2003) [78]	4 wk	150 mg/d			
		HAM-A	−0.10	(−0.46, 0.26)	NS
		HAM-D	−0.15	(−0.74, 0.44)	NS
		600 mg/d			
		HAM-A	−0.47	(−0.84, −0.10)	0.013
		HAM-D	−0.74	(−1.35, −0.14)	0.016
Rickels et al. (2005) [80]	4 wk	300 mg/d			
		HAM-A	−0.52	(−0.82, −0.22)	<0.001
		HAM-D	−0.95	(−1.41, −0.49)	<0.001
		450 mg/g			
		HAM-A	−0.47	(−0.76, −0.17)	0.002
		HAM-D	−0.57	(−1.03, −0.11)	0.016
		600 mg/d			
		HAM-A	−0.54	(−0.84, −0.24)	<0.001
		HAM-D	−0.67	(−1.14, −0.21)	0.005
Pohl et al. (2005) [79]	6 wk	200 mg/d			
		HAM-A	−0.41	(−0.71, −0.10)	0.010
		HAM-D	−0.81	(−1.28, −0.34)	<0.001
		400 mg/d			
		HAM-A	−0.48	(−0.78, −0.19)	0.002
		HAM-D	−0.81	(−1.25, −0.36)	<0.001
		450 mg/d			
		HAM-A	−0.50	(−0.80, −0.20)	0.001
		HAM-D	−0.84	(−1.28, −0.40)	<0.001
Montgomery et al. (2006) [81]	6 wk	400 mg/d			
		HAM-A	−0.54	(−0.80, −0.29)	<0.001
		HAM-D	−0.75	(−1.10, −0.39)	<0.001
		600 mg/d			
		HAM-A	−0.57	(−0.82, −0.32)	<0.001
		HAM-D	−0.74	(−1.09, −0.39)	<0.001
Montgomery et al. (2008) [82]	8 wk	150–600 mg/d			
		HAM-A	−0.43	(−0.69, −0.18)	0.001
		HAM-D	−0.58	(−0.98, −0.18)	0.005
Kasper et al. (2009) [76]	8 wk	300–600 mg/d			
		HAM-A	−0.36	(−0.62, −0.10)	0.008
		HAM-D	−0.41	(−0.75, −0.06)	0.021

GAD: generalized anxiety disorder; HAM-A: Hamilton anxiety instrument; HAM-D: Hamilton depression instrument.
[a] HAM-A insomnia factor scores range from 0 = "none" to 4 = "very severe".
[b] HAM-D insomnia factor scores range from 0 to 6, with higher scores indicating greater sleep disturbance.

Direct effects of pregabalin on sleep in GAD

Two GAD studies support a direct effect of pregabalin on sleep itself, distinct from its anxiolytic activity. In one study [76], pregabalin improved the MOS-SS sleep disturbance subscale (see above) and path analysis estimated that a large proportion (~53%) of this effect was a direct effect of pregabalin on sleep itself [86]. Further evidence for a direct effect of pregabalin on sleep comes from a study in patients undergoing benzodiazepine withdrawal [87]. Twelve weeks of flexible-dose pregabalin improved the MOS-SS overall sleep problems index by 55%, and this effect was significant in withdrawal failures (those who still had benzodiazepine in their urine), arguing against the possibility that benzodiazepine withdrawal itself could have improved sleep. Furthermore, the effects of pregabalin on the sleep problems index score were significant in patients who still exhibited high levels of anxiety at study endpoint, arguing against the theory that improvements in anxiety may have accounted for the improved MOS-SS scores.

Practice points

In trials of GAD:

1) conclusions are limited due to a lack of polysomnography data;
2) pregabalin (150–600 mg/d) significantly improved Hamilton anxiety instrument insomnia scores;
3) pregabalin (300–600 mg/d) significantly improved Hamilton depression instrument insomnia scores in patients with particularly high levels of insomnia at baseline;
4) evidence suggests that pregabalin has a direct effect on sleep, distinct from its anxiolytic activity.

Healthy volunteers

In a three-way crossover, healthy subjects ($n = 23$) received 450 mg/d pregabalin, 3 mg/d alprazolam and placebo for one day each [88]. Treatment order was randomized for each patient and PSG was performed each night. Pregabalin increased the time spent in slow-wave sleep (38%) compared with placebo (26%), total sleep time (+26 min), the number of awakenings, sleep onset latency (−7 min) and sleep efficiency (+5%) were also improved. Although there were no differences in total sleep time between pregabalin and alprazolam, pregabalin increased the amount of slow-wave sleep compared with alprazolam.

Discussion

Pregabalin consistently improved patient-reported assessments of sleep quality in a dose-related manner in most clinical conditions examined, with the exception of partial seizures. Furthermore, this dose relationship generally held true for doses above 300 mg/d (i.e., 300 < 450 < 600 mg/d) in patients with neuropathic pain and, in particular, patients with FM. Improvements were often evident at the first evaluation following initiation of treatment and were sustained throughout the treatment period.

In PSG studies, pregabalin treatment typically improved wake time after sleep onset (DPN, FM and RLS), the number of awakenings (FM and partial seizures) and time spent in slow-wave sleep (FM, RLS and partial seizures). Decreased stage 1 sleep was also commonly found (RLS and partial seizures). Decreased latency to persistent sleep was evident in FM patients but this effect was small relative to the effects on wake time after sleep onset, suggesting that pregabalin predominantly affects sleep maintenance. Findings of fewer awakenings, more time spent in slow-wave sleep and less time spent in stage 1 sleep demonstrate that pregabalin consolidates sleep by increasing “depth of sleep”. These PSG findings may be related to patient reports of improved sleep quality with pregabalin treatment.

Gabapentin, like pregabalin, is an $\alpha_2\delta$ ligand used to treat seizures and neuropathic pain. A number of RLS studies demonstrate that gabapentin and gabapentin enacarbil (a gabapentin prodrug) have a positive effect on patient-reported measures of sleep [89–92]. PSG documents that gabapentin improves total sleep time [89,91], sleep efficiency [89,91] and wake time after sleep onset [90,91]. Similar to pregabalin, gabapentin also consistently decreased the amount of stage 1 sleep while enhancing slow-wave sleep [89–91]. Like pregabalin, gabapentin also enhances slow-wave sleep in patients with epilepsy [63] and in healthy adults [92]. In one small PSG study in patients with primary insomnia, gabapentin increased sleep efficiency and slow-wave sleep, which was accompanied by a decrease in wake time after sleep onset [93]. There are no published studies of pregabalin for the treatment of primary insomnia.

Although no studies directly compare pregabalin and gabapentin, the general effects of the two are similar. The most interesting and unique effects of pregabalin and gabapentin are their effects on slow-wave sleep and the associated sleep consolidation, which differentiate them from classical sedating drugs such as benzodiazepine receptor agonists (BZRAs). As we have reviewed, pregabalin and gabapentin are most often associated with an increase in slow-wave sleep. In contrast, BZRAs predominantly affect stage 2 sleep and typically suppress, or have little effect on, slow-wave sleep [94]. Further, BZRAs primarily act on sleep induction with lesser effects on sleep maintenance [94]. While some improvement in sleep onset has been observed with pregabalin, these effects are minor relative to the observed improvement in sleep maintenance parameters.

The analgesic, anxiolytic and anticonvulsant effects of pregabalin, are attributed to binding at the $\alpha_2\delta$ subunit of neuronal voltage-gated calcium channels, which results in modulation of neurotransmitter release from hyper-excited pre-synaptic neurons [95]. It is possible that the sleep benefits exhibited by pregabalin, and gabapentin, are also due to $\alpha_2\delta$ binding activity. However, the precise mechanism by which pregabalin, and gabapentin, affect sleep are currently unknown. Further, it may be that multiple mechanisms contribute to pregabalin’s, and gabapentin’s, overall sleep benefit.

Pregabalin’s sleep benefit is likely the result of both direct effects on sleep itself and indirect effects on sleep mediated through improvements in the comorbid condition. Often the relationship between sleep disturbance and the comorbid condition is overlooked and it is assumed, mistakenly, that treating the comorbid condition will resolve the sleep problem. This assumption; however, does not account for the exacerbating effect disturbed sleep has on factors such as pain, depression and anxiety. It is, therefore, recommended that treatment strategies focus on both the comorbid condition as well as the associated sleep disturbance. The data reviewed here suggest that, in certain conditions, pregabalin has positive effects on both the comorbid condition and the disturbed sleep itself.

Most of the studies reviewed utilized a treatment schedule where the total daily dose of pregabalin was achieved through equal twice daily (morning and evening) or three times daily (morning, afternoon and evening) dosing. The exception was in trials of RLS, where patients received a single dose of pregabalin 1–3 h before bedtime [59] or received a majority of their total daily dose of pregabalin 2 h prior to bedtime [58] (for patients receiving 450 mg/d). Thus, for most studies, patients received at least half of their total daily dose of pregabalin during the daytime hours. Despite this dosing schedule, most patients still experienced a sleep benefit during the night-time hours. These findings are consistent with PSG results suggesting that pregabalin primarily affects sleep maintenance rather than sleep initiation.

In randomized clinical trials, the most common adverse reactions associated with pregabalin (≥5% and twice placebo) are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain and thinking abnormal (primarily difficulty with concentration/attention) [96]. Daytime somnolence was reported by 23% of pregabalin-treated patients compared to 8% for placebo. Generally, the onset of somnolence occurred shortly after the initiation of treatment and occurred more frequently at higher doses. In short-term trials, somnolence persisted until the last dose of pregabalin treatment in 42% of patients who experienced this particular event. However, most instances of somnolence are mild to moderate in severity [96] and patients experience little disruption to daytime functioning [97]. This also differentiates pregabalin from BZRAs, since the use of BZRAs often results in increased daytime sedation and impaired cognitive/psychomotor functioning.

A few limitations of this review need to be acknowledged. Our ability to directly compare the effects of pregabalin on disturbed sleep across patient populations is constrained by the fact that different assessment tools were used for each population and no studies directly compared different conditions. The primary sleep assessment tool in trials of neuropathic pain, for example, was the DSIS, while trials in FM patients utilized the DSQD. Likewise, trials in RLS patients primarily used the subjective sleep questionnaire and the MOS-SS, while trials in GAD patients employed the HAM-A or HAM-D instruments. Thus, although pregabalin consistently improved patient-reported measures of sleep in these different patient populations, it is difficult to determine whether pregabalin is significantly more effective at improving sleep in one particular population versus another. Our conclusions are also somewhat

limited by a dearth of PSG data. Of the approximately 50 studies reviewed, only six used PSG to assess sleep (neuropathic pain = 1; FM = 1; RLS = 1; epilepsy = 2; healthy = 1). Finally, though the data reveal a direct effect of pregabalin on sleep itself, it is difficult to speculate the relative extent to which direct and indirect treatment effects contribute to pregabalin's overall sleep benefit and it is likely these contributions vary across different comorbidities. Despite these constraints; however, the data here demonstrate a significant sleep benefit in response to pregabalin treatment.

Practice points

The data in this review show that:

1) patients report improved sleep quality in response to pregabalin across several different clinical conditions;
2) polysomnography reveals fewer awakenings, more time spent in slow-wave sleep and less time spent in stage 1 sleep, suggesting that pregabalin consolidates fragmented sleep and increases depth of sleep;
3) evidence suggests that pregabalin has a direct effect on sleep that is distinct from its analgesic, anxiolytic and anticonvulsant effects;
4) pregabalin and gabapentin exhibit similar effects on sleep, suggesting that these effects are due to their ability to modulate the $\alpha_2\delta$ subunit of neuronal voltage-gated calcium channels.

Research agenda

In the future we need:

1) further polysomnographic studies to confirm the precise sleep benefits provided by $\alpha_2\delta$ ligands;
2) further studies directly comparing the effects of pregabalin in different patient populations;
3) further preclinical/clinical research to elucidate the mechanism(s), both direct and indirect, underlying pregabalin's sleep benefit;
4) further studies of $\alpha_2\delta$ ligands in patients with primary insomnia.

Conflicts of interest

A. Clair and M. Resnick are full-time employees of Pfizer Inc. T. Roth has received research funding from Aventis, Cephalon, GlaxoSmithKline, Merck, Neurocrine, Pfizer Inc., Sanofi-Aventis, Schering-Plough, Sepracor, Somaxon, Somnus, Syrex, Takeda, TransOral, Ventus, Wyeth and Xenoport; has acted as a consultant or served on an advisory board for Abbott, Accadia, Acogolix, Acorda, Actelion, Addrenex, Alchemers, Alza, Ancel, Arena, AstraZeneca, Aventis, AVER, Bayer, BMS, BTG, Cephalon, Cypress, Dove, Eisai, Elan, Eli Lilly, Evotec, Forest, GlaxoSmithKline, Hypnion, Impax, Intec, Intra-Cellular, Jazz, Johnson & Johnson, King, Lundbeck, McNeil, MediciNova, Merck, Neurim, Neurocrine, Neurogen, Novartis, Ocera, Orexo, Organon, Otsuka, Prestwick, Proctor and Gamble, Pfizer Inc., Purdue, Resteva, Roche, Sanofi-Aventis, Sepracor, Servier, Shire, Somaxon, Somnus, Steady Sleep Rx, Syrex, Takeda, TransOral, Transcept, Vanda, Ventus, Vivometrics, Wyeth, Xenoport and Yamanuchi and participated in Speakers' Bureau for Cephalon, Sanofi-Aventis and Sepracor. L. Arnold has received grants/research support from Boehringer Ingelheim (past), Forest Laboratories, Eli Lilly, Novartis (past), Sanofi-Synthelabo (past), Allergan (past), Theravance, AstraZeneca, Takeda, and Pfizer Inc, and has been a consultant for AstraZeneca (past), Sepracor (past), Allergan (past), Vivus (past), Boehringer Ingelheim (past), Organon (past), Forest Laboratories (past), Eli Lilly (past), Grunenthal (past), Johnson & Johnson (past), Pfizer Inc., Sanofi-Synthelabo (past), Daiichi Sankyo, Theravance, Dainippon Sumitomo, Purdue, and Takeda (past), and has been on the Speakers' Bureau for Eli Lilly (past), Forest (past), and Pfizer. D. Garcia-Borreguero has served on scientific advisory boards for, and received speaker honoraria from, Boehringer Ingelheim, GlaxoSmithKline, Jazz Pharmaceuticals, Lundbeck, Merck & Co, Pfizer Inc., Sanofi-Aventis, Engage and XenoPort. All external authors (T.R., L.M.A., and D.Gb) were invited, by Pfizer, to help write this review. The external authors did not receive any compensation related to the development of this manuscript, were provided full access to all data, and approved the final version prior to submission. Editorial and medical writing support was provided by Matt Soulsby, PhD, at Engage Scientific Solutions and was funded by Pfizer Inc.

References

[1] Hays RD, Stewart AL. Sleep measures. In: Stewart AL, Ware JE, editors. Measuring functioning and well being. Durham, NC: Duke University Press; 1992. p. 235–59.
[2] Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–5.
[3] Hamilton M. Development of a rating scale for primary depressive illness. Br J Clin Psychol 1967;6:278–96.
[4] Vranken JH. Mechanisms and treatment of neuropathic pain. Cent Nerv Syst Agents Med Chem 2009;9:71–8.
[5] Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. Diabetes Res Clin Pract 2000;47:123–8.
[6] Widerstrom-Noga EG, Felipe-Cuervo E, Yezierski RP. Chronic pain after spinal injury: interference with sleep and daily activities. Arch Phys Med Rehabil 2001;82:1571–7.
[7] Oster G, Harding G, Dukes E, Edelsberg J, Cleary PD. Pain, medication use, and health-related quality of life in older persons with postherpetic neuralgia: results from a population-based survey. J Pain 2005;6:356–63.
[8] Mundel T, Martin S, LaMoreaux L, Hotary L, Roth T. Polysomnographic evaluation of sleep disturbance in neuropathic pain. Sleep 2003;26(abstract suppl.):A354.
*[9] Boyle J, Eriksson ME, Gribble L, Gouni R, Johnsen S, Coppini DV, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care 2012;35:2451–8.
[10] Richter RW, Portenoy R, Sharma U, LaMoreaux L, Bockbrader H, Knapp LE. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. J Pain 2005;6:253–60.
[11] Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 2004;63:2104–10.
[12] Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004;110:628–38.
[13] Tölle T, Freynhagen R, Versavel M, Trostmann U, Young Jr JP. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: a randomized, double-blind study. Eur J Pain 2008;12:203–13.
[14] Arezzo JC, Rosenstock J, Lamoreaux L, Pauer L. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. BMC Neurol 2008;8:33.
[15] Satoh J, Yagihash S, Baba M, Suzuki M, Arakawa A, Yoshiyama T, et al. Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14-week randomized, double-blind, placebo-controlled trial. Diabet Med 2011;28:109–16.
[16] Sabatowski R, Gálvez R, Cherry DA, Jacquot F, Vincent E, Maisonobe P. Pregabalin reduces pain and improves sleep and mood disturbances in patients

* The most important references are denoted by an asterisk.

with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. Pain 2004;109:26–35.
[17] Dworkin RH, Corbin AE, Young Jr JP, Sharma U, LaMoreaux L, Bockbrader H, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003;60:1274–83.
[18] van Seventer R, Feister HA, Young Jr JP, Stoker M, Versavel M, Rigaudy L. Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. Curr Med Res Opin 2006;22:375–84.
[19] Stacey B, Barrett JA, Whalen E, Phillips KF, Rowbotham M. Pregabalin for postherpetic neuralgia: placebo-controlled trial of fixed and flexible dosing regimens on allodynia and time to onset of pain relief. J Pain 2008;9:1006–17.
[20] Ogawa S, Suzuki M, Arakawa A, Araki S, Yoshiyama T. Evaluation of the efficacy and safety of pregabalin in the treatment of postherpetic neuralgia – a randomized, double-blind, multicenter, placebo-controlled study. J Jpn Soc Pain Clin 2010;17:141–52.
[21] Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005;115:254–63.
[22] Baron R, Brunnmüller U, Brasser M, May M, Binder A. Efficacy and safety of pregabalin in patients with diabetic peripheral neuropathy or postherpetic neuralgia: open-label, non-comparative, flexible-dose study. Eur J Pain 2008;12:850–8.
[23] Guan Y, Ding X, Cheng Y, Fan D, Tan L, Wang Y, et al. Efficacy of pregabalin for peripheral neuropathic pain: results of an 8-week, flexible-dose, double-blind, placebo-controlled study conducted in China. Clin Ther 2011;33:159–66.
[24] Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology 2006;67:1792–800.
[25] Cardenas DD, Neishoff EC, Suda K, Goto S, Sanin L, Kaneko T, et al. A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. Neurology 2013;80:533–9.
[26] Saldaña MT, Navarro A, Pérez C, Masramón X, Rejas J. Patient-reported-outcomes in subjects with painful lumbar or cervical radiculopathy treated with pregabalin: evidence from medical practice in primary care settings. Rheumatol Int 2010;30:1005–15.
[27] Baron R, Freynhagen R, Tolle T, Cloutier C, Leon T, Murphy TK, et al. The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy. Pain 2010;150:420–7.
[28] Kim JS, Bashford G, Murphy TK, Martin A, Dror V, Cheung R. Safety and efficacy of pregabalin in patients with central post-stroke pain. Pain 2011;152:1018–23.
[29] van Seventer R, Bach F, Toth C, Serpell M, Temple J, Murphy TK, et al. Pregabalin in the treatment of posttraumatic peripheral neuropathic pain: a randomized double-blind trial. Eur J Neurol 2010;17:1082–9.
[30] Mañas A, Ciria JP, Fernández MC. Post hoc analysis of pregabalin vs. non-pregabalin treatment in patients with cancer-related neuropathic pain: better pain relief, sleep and physical health. Clin Transl Oncol 2011;13:656–63.
[31] Perez C, Navarro A, Saldana MT, Martinez S, Rejas J. Patient-reported outcomes in subjects with painful trigeminal neuralgia receiving pregabalin: evidence from medical practice in primary care settings. Cephalalgia 2009;29:781–90.
[32] Simpson DM, Schifitto G, Clifford DB, Murphy TK, Durso-De Cruz E, Glue P, et al. Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. Neurology 2010;74:413–20.
[33] Xochilcal-Morales M, Manuel Castro E, Aniceto Guajardo-Rosas J, Nava Obergon T, Acevedo J, Gavidia Chucan M, et al. A prospective, open-label, multicentre study of pregabalin in the treatment of neuropathic pain in Latin America. Int J Clin Pract 2010;64:1301–9.
[34] Moon DE, Lee DI, Lee SC, Song SO, Yoon DM, Yoon MH, et al. The efficacy and safety of pregabalin using a flexible, optimized dose schedule in subjects with peripheral neuropathic pain: a 10-week, randomized, double-blind, placebo-controlled, multicenter study. Clin Ther 2010;32:2370–85.
[35] Anastassiou E, Iatrou CA, Vlaikidis N, Vafiadou M, Stamatiou G, Plesia E, et al. Impact of pregabalin treatment on pain, pain-related sleep interference and general well-being in patients with neuropathic pain: a non-interventional, multicentre, post-marketing study. Clin Drug Investig 2011;31:417–26.
[36] Lyrica Study Group. Pregabalin for peripheral neuropathic pain: results of a multicenter, non-comparative, open-label study in Indian patients. Int J Clin Pract 2006;60:1060–7.
[37] Gilron I, Wajsbrot D, Therrien F, Lemay J. Pregabalin for peripheral neuropathic pain: a multicenter, enriched enrollment randomized withdrawal placebo-controlled trial. Clin J Pain 2011;27:185–93.
[38] Toelle TR, Varvara R, Nimour M, Emir B, Brasser M. Pregabalin in neuropathic pain related to DPN, cancer and back pain: analysis of a 6-week observational study. Open Pain J 2012;5:1–11.
[39] Perez-Lloret S, Rojas GM, Menoni MC, Ruiz G, Velasquez C, Rodriguez H, et al. Pregabalin beneficial effects on sleep quality or health-related quality of life are poorly correlated with reduction on pain intensity after an 8-week treatment course. Clin Neuropharmacol 2012;35:21–4.
[40] van Seventer R, Serpell M, Bach F, Morlion B, Zlateva G, Bushmakin AG, et al. Relationships between changes in pain severity and other patient-reported outcomes: an analysis in patients with posttraumatic peripheral neuropathic pain. Health Qual Life Outcomes 2011;9.
[41] Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 2010;62:600–10.
[42] Harding SM. Sleep in fibromyalgia patients: subjective and objective findings. Am J Med Sci 1998;315:367–76.
[43] Branco J, Atalaia A, Paiva T. Sleep cycles and alpha-delta sleep in fibromyalgia syndrome. J Rheumatol 1994;21:1113–7.
[44] Rizzi M, Sarzi-Puttini P, Atzeni F, Capsoni F, Andreoli A, Pecis M, et al. Cyclic alternating pattern: a new marker of sleep alteration in patients with fibromyalgia? J Rheumatol 2004;31:1193–9.
*[45] Roth T, Lankford A, Bhadra P, Whalen E, Resnick EM. Effect of pregabalin on sleep in patients with fibromyalgia and sleep maintenance disturbance: a randomized, placebo-controlled, 2-way crossover polysomnography study. Arthritis Care Res (Hoboken) 2012;64:597–606.
[46] Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, et al., Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:1264–73.
[47] Mease PJ, Russell IJ, Arnold L, Florian H, Young Jr JP, Martin SA, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol 2008;35:502–14.
[48] Arnold LM, Russell IJ, Diri EW, Duan WR, Young JP, Sharma U, et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. J Pain 2008;9:792–805.
[49] Pauer L, Winkelmann A, Arsenault P, Jespersen A, Whelan L, Atkinson G, et al. An international, randomised, double-blind, placebo-controlled, phase III trial of pregabalin monotherapy in the treatment of patients with fibromyalgia. J Rheumatol 2011;38:2643–52.
[50] Straube S, Derry S, Moore RA, McQuay HJ. Pregabalin in fibromyalgia – meta-analysis of efficacy and safety from company clinical trial reports. Rheumatology (Oxford) 2010;49:706–15.
[51] Russell IJ, Crofford LJ, Cappelleri J, Bushmakin A, Sadosky A, Leon T, et al. The effect of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. Sleep Med 2009;10:604–10.
[52] Emir B, Murphy K, Petersel D, Whalen E. Treatment response to pregabalin in fibromyalgia: effect of patient baseline characteristics. Expert Opin Pharmacother 2010;11:2275–80.
[53] Moore RA, Straube S, Paine J, Phillips C, Derry S, McQuay HJ. Fibromyalgia: moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain. Pain 2010;149:360–4.
[54] Ekbom KA. Restless legs syndrome. Acta Med Scand 1945;158(Suppl.):122.
[55] Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep Med 2004;5:237–46.
[56] Hornyak M, Feige B, Voderholzer U, Philipsen A, Riemann D. Polysomnography findings in patients with restless legs syndrome and in healthy controls: a comparative observational study. Sleep 2007;30:861–5.
[57] Allen R, Becker PM, Bogan R, Schmidt M, Kushida CA, Fry JM, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. Sleep 2004;27:907–14.
*[58] Garcia-Borreguero D, Larrosa O, Williams AM, Albares J, Pascual M, Palacios JC, et al. Treatment of restless legs syndrome with pregabalin: a double-blind, placebo-controlled study. Neurology 2010;74:1897–904.
[59] Allen R, Chen C, Soaita A, Wohlberg C, Knapp L, Peterson BT, et al. A randomized, double-blind, 6-week, dose-ranging study of pregabalin in patients with restless legs syndrome. Sleep Med 2010;11:512–9.
[60] de Weerd A, de Haas S, Otte A, Trenité DK, van Erp G, Cohen A, et al. Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life. Epilepsia 2004;45:1397–404.
[61] Touchon J, Baldy-Moulinier M, Billiard M, Besset A, Cadhillac J. Sleep organization and epilepsy. Epilepsy Res 1991;2:73–81.
[62] Bazil CW. Epilepsy and sleep disturbance. Epilepsy Behav 2003;4(Suppl. 2):S39–45.
[63] Legros B, Bazil CW. Effects of antiepileptic drugs on sleep architecture: a pilot study. Sleep Med 2003;4:51–5.
[64] Romigi A, Izzi F, Marciani MG, Torelli F, Zannino S, Pisani LR, et al. Pregabalin as add-on therapy induces REM sleep enhancement in partial epilepsy: a polysomnographic study. Eur J Neurol 2009;16:70–5.
[65] de Haas S, Otte A, de Weerd A, van Erp G, Cohen A, van Gerven J. Exploratory polysomnographic evaluation of pregabalin on sleep disturbance in patients with epilepsy. J Clin Sleep Med 2007;3:473–8.
[66] Bazil CW, Dave J, Cole J, Stalvey J, Drake E. Pregabalin increases slow-wave sleep and may improve attention in patients with partial epilepsy and insomnia. Epilepsy Behav 2012;23:422–5.
[67] Lee BI, Yi S, Hong SB, Kim M-K, Lee SA, Lee SK, et al. Pregabalin add-on therapy using a flexible, optimized dose schedule in refractory partial epilepsies: a double-blind, randomized, placebo-controlled, multicenter trial. Epilepsia 2009;50:464–74.
[68] Rivera-Castaño L, Leal-Cantu R, Abreu P, Guerrero M, Davila G. A 21-week open-label clinical trial of pregabalin as an add-on therapy in partial seizures at multiple centers in Mexico (PREPS Mexico). Epilepsy Res 2012;100:74–9.

[69] Sancho J, Ivanez V, Molins A, Lopez Gomez V, Masramon X, Perez M. Changes in seizures severity and quality of life in patients with refractory partial epilepsy. Epilepsy Behav 2010;19:409–13.
[70] Tsounis S, Kimiskidis V, Kazis D, Gkiatas K, Garganis K, Karageorgiou K, et al. An open-label, add-on study of pregabalin in patients with partial seizures: a multicenter trial in Greece. Seizure 2011;20:701–5.
[71] Ryvlin P, Kalviainen R, Von Raison F, Giordano S, Emir B. Pregabalin in partial seizures: a pragmatic 21-week, open-label study (PREPS). Eur J Neurol 2010;17:726–32.
[72] Papadimitriou GN, Linkowski P. Sleep disturbance in anxiety disorders. Int Rev Psychiatry 2005;17:229–36.
[73] Johnson EO, Roth T, Breslau N. The association of insomnia with anxiety disorders and depression: exploration of the direction of risk. J Psychiatr Res 2006;40:700–8.
[74] Monti JM, Monti D. Sleep disturbance in generalized anxiety disorder and its treatment. Sleep Med Rev 2000;4:263–76.
[75] Fuller KH, Waters WF, Binks PG, Anderson T. Generalized anxiety and sleep architecture: a polysomnographic investigation. Sleep 1997;20:370–6.
[76] Kasper S, Herman B, Nivoli G, Van Ameringen M, Petralia A, Mandel F, et al. Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: results of a double-blind, placebo-controlled 8-week trial. Int Clin Psychopharmacol 2009;24:87–96.
[77] Feltner DE, Crockatt JG, Dubovsky SJ, Cohn CK, Shrivastava RK, Targum SD, et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. J Clin Psychopharmacol 2003;23:240–9.
[78] Pande AC, Crockatt JG, Feltner DE, Janney CA, Smith WT, Weisler R, et al. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. Am J Psychiatry 2003;160:533–40.
[79] Pohl RB, Feltner DE, Fieve RR, Pande AC. Efficacy of pregabalin in the treatment of generalized anxiety disorder: double-blind, placebo-controlled comparison of BID versus TID dosing. J Clin Psychopharmacol 2005;25:151–8.
[80] Rickels K, Pollack MH, Feltner DE, Lydiard RB, Zimbroff DL, Bielski RJ, et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry 2005;62:1022–30.
[81] Montgomery SA, Tobias K, Zornberg GL, Kasper S, Pande AC. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine. J Clin Psychiatry 2006;67:771–82.
[82] Montgomery S, Chatamra K, Pauer L, Whalen E, Baldinetti F. Efficacy and safety of pregabalin in elderly people with generalised anxiety disorder. Br J Psychiatry 2008;193:389–94.
[83] Feltner D, Wittchen HU, Kavoussi R, Brock J, Baldinetti F, Pande AC. Long-term efficacy of pregabalin in generalized anxiety disorder. Int Clin Psychopharmacol 2008;23:18–28.
[84] Lydiard RB, Rickels K, Herman B, Feltner DE. Comparative efficacy of pregabalin and benzodiazepines in treating the psychic and somatic symptoms of generalized anxiety disorder. Int J Neuropsychopharmacol 2010;13:229–41.
[85] Montgomery SA, Herman BK, Schweizer E, Mandel FS. Efficacy of pregabalin and benzodiazepines in generalized anxiety disorder presenting with high levels of insomnia. Int Clin Psychopharmacol 2009;24:214–22.
[86] Bollu V, Bushmakin A, Cappelleri J, Chen C, Feltner D, Wittchen H. Pregabalin reduces sleep disturbance in patients with generalized anxiety disorder via both direct and indirect mechanisms. Eur J Psychiatry 2010;24:18–27.
[87] Rubio G, Bobes J, Cervera G, Teran A, Perez M, Lopez-Gomez V, et al. Effects of pregabalin on subjective sleep disturbance symptoms during withdrawal from long-term benzodiazepine use. Eur Addict Res 2011;17:262–70.
*[88] Hindmarch I, Dawson J, Stanley N. A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep 2005;28:187–93.
[89] Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology 2002;59:1573–9.
[90] Kushida CA, Walters AS, Becker P, Thein SG, Perkins AT, Roth T, et al. A randomized, double-blind, placebo-controlled, crossover study of XP13512/GSK1838262 in the treatment of patients with primary restless legs syndrome. Sleep 2009;32:159–68.
[91] Winkelman JW, Bogan RK, Schmidt MH, Hudson JD, DeRossett SE, Hill-Zabala CE. Randomized polysomnography study of gabapentin enacarbil in subjects with restless legs syndrome. Mov Disord 2011;26:2065–72.
[92] Foldvary-Schaefer N, De Leon Sanchez I, Karafa M, Mascha E, Dinner D, Morris HH. Gabapentin increases slow-wave sleep in normal adults. Epilepsia 2002;43:1493–7.
[93] Lo H, Yang C, Lo HG, Lee C, Ting H, Tzang B. Treatment effects of gabapentin for primary insomnia. Clin Neuropharmacol 2010;33:84–90.
[94] Walsh JK, Roth T. Pharmacologic treatment of insomnia: benzodiazepine receptor agonists. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 5th ed. St. Louis, MO: Elsevier Saunders; 2011. p. 905–15.
[95] Dooley DJ, Taylor CP, Donevan S, Feltner D. Ca2+ channel alpha2delta ligands: novel modulators of neurotransmission. Trends Pharmacol Sci 2007;28:75–82.
[96] Lyrica US prescribing information [online]. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=561 [accessed 01.07.13].
[97] Pauer L, Atkinson G, Murphy TK, Petersel D, Zeiher B. Long-term maintenance of response across multiple fibromyalgia symptom domains in a randomized withdrawal study of pregabalin. Clin J Pain 2012;7:609–14.